

## ABSTRACT

**Background:** Chemotherapeutic drug like adriamycin, doxorubicin, idarubicin, epirubicin, and mitoxantrone are associated with acute, reversible cardiotoxic effects and a dose-related cardiac dysfunction/Cardiomyopathy. This entity is largely irreversible and cumulative and prevention is the most preferred strategy. Development of the same can be largely averted by monitoring the left ventricular function by easily reproducible methods available with us as like 2D-Echocardiography. The incidence of Anthracycline induced cardiomyopathy (AIC) is in the range of 3-5% for clinical and 24-27% in Indian population.(Khattry et al., 2009) As not everyone who receives anthracyclines develop cardiotoxicity, the identification of a predictive test is required. A number of biomarkers like Troponin I, Creatine kinase -MB have been investigated to assess their utility as a potential biomarker for predicting the risk of developing Anthracycline induced Cardiomyopathy (AIC), but none have proved effective. The identification of a test that would predict patients likely to develop AIC would be particularly valuable in India given the high prevalence of subclinical cardiac dysfunction due to other causes such as diabetes mellitus. In this context a genetic study of Cardiomyopathy in Indian population found a specific 25- base pair deletion in the gene MYBPC3, which encodes Cardiac myosin binding protein C, a key constituent of cardiac sarcomere, This was

prevalent more commonly in the South Indian population.(Dhandapany et al., 2009). DNA extraction was performed from peripheral blood sample of 18 patients with documented AIC which was followed by PCR, Gel electrophoresis and Restriction digestion to look for the same specific 25-bp deletion in MYBPC3 gene

## **RESULTS.**

Analysis of outcomes of diffuse large B cell lymphoma and high grade follicular lymphoma treated with CHOP-based chemotherapy between 2010- 2013:

The evaluable patients (n=227) with DLBCL and Grade 3 FL with chemotherapy regimen CHOP with or without Rituximab were included in the analysis. All patients were followed up until December 2014. A median follow up was 2.6 years. Majority of the patients 77% were below 60 years at presentation. 65% patients were males and 35% were females. B symptoms were present in (32%) of the patients at presentation. 70 percent of patients presented in PS-1. Cervical lymphadenopathy was the most common presentation. Extranodal involvement was seen 23% of the patients and Gastrointestinal system was the most common extranodal site. 55 % of patients presented with stage III and IV disease and 37% patients had High risk IPI score. 52 % patients received RCHOP and 48 percent received CHOP. After treatment, 64% of patients CR and 20 percent were in partial

remission after all treatment.,Fifty five patients had Primary progressive disease.

In Univariate analysis, Patients with ECOG PS 0,1 had a better 3 year EFS and OS as compared to patients presenting with Poor ECOG PS( $p<0.004$ ). Patient presenting with Stage 1, 2 had a better outcome than patients presenting with stage 3 and 4( $p<0.001$ ) .Patient with Low risk IPI score had better 3 year EFS and OS as compared to a higher IPI . Number of extranodal sites and Serum LDH did not have any significant impact on the outcome( $p$  value 0.998 &0.114 respectively).

In multivariate analysis: model 1, where PS, Stage, LDH and chemotherapy were evaluated. Only chemotherapy (HR:1.991;CI:1.227-3.233, $p$  value $<0.005$ ) and PS(HR:2.04 ;CI 1.256-3.315, $p$  value $< 0.004$  were significant. In model 2, where LDH was excluded, stage, PS(HR:2.4,CI:1.256- 3.315,  $p<0.004$ )and type of chemotherapy were significant (HR 1.991,CI:1.227-3.233  $p< 0.005$ )

A separate analysis of 18 cases with Anthracycline induced Cardiomyopathy showed that Of the 18, MYBPC3 was detected using PCR in 8 samples. The remaining samples were not analysable poor quality of DNA. A 928 base pair band was observed in all 8 samples which suggested the absence of 25 base pair deletion in any of these samples. This was further confirmed by a restriction digestion analysis using Bgl1 enzyme, which gave

a distinct restriction banding pattern as expected if MYBPC3 was wild type. In this group of 8 patients who had a satisfactory PCR there was no polymorphism (del 25bp) in the MYBPC3 gene.

### **Conclusion of the study:**

By Univariate analysis, Performance Status, IPI score, and type of chemotherapy predicted survival. Most of these indirectly reflect the stage at presentation. Stage is probably the single most important predictor of survival in DLBCL. Older age at presentation(>60 years), Presence of more than one extranodal site and a Higher LDH at presentation were not found significant in Multivariate analysis. Twenty Five base pair deletion in the gene-MYBPC3 which is indigenous to the cases with Cardiomyopathy in South Indians does not seem to responsible for development or worsening of Anthracycline induced cardiotoxicity.

**Keywords :** DLBCL:Diffuse large B cell lymphoma, MYBPC3:Myosin binding protein C3, AIC: Anthracycline induced Cardiomyopathy, DCM:Dilated cardiomyopathy.